

REMARKS

Claims 1-3, 5-6, 9-11, 19-21, 23-24, and 27-29 are pending.

**I. Rejection under 35 U.S.C. §112, 2<sup>nd</sup> paragraph**

Examiner rejects claim 39 as indefinite with respect to the limitation, "non-steroidal anti-inflammatory agent" under §112, 2<sup>nd</sup> paragraph. Applicant has cured such defect by way of amendment and respectfully requests Examiner withdraw the rejection of record with respect to claim 39.

**II. Rejections under 35 U.S.C. §103**

Examiner rejects all claims as being unpatentable over Hewitt et al., Lozada and Sharpe et al., in view of Batt et al. Examiner alleges the employment of these teachings concomitantly in a method useful for the very same purpose would be seen as prima facie obvious, absent evidence to the contrary. For the reasons submitted below, Applicant respectfully traverses Examiner's rejection and requests Examiner withdraw the §103 rejection, as there is no suggestion or motivation to combine the cited references and the references in fact teach away from the present application.

Hewitt et al. describes compositions comprising several elements in order to be effective. Specifically, at column 6, lines 13-26, Hewitt describes the embodiments of the claimed invention, ranging from cyclosporine A ("CsA") as a cream to combinations involving CsA and different immunosuppressants and anti-inflammatory agents. In fact, the entire specification is dedicated to

formulating a combination therapy approach in order to engage in site-specific immune suppression of immune/inflammatory responses with combinations of immunosuppressants and anti-inflammatory compounds. See Abstract, in particular.

The present invention, on the other hand, specifically claims azathioprine as the desired therapeutic. This is in stark contrast to Hewitt et al. necessitating using formulations in tandem with systemic applications of immunosuppressants such as CsA. The crux of Hewitt et al. essentially precludes use of only one immunosuppressant in the claimed formulation.

Furthermore, there would be no motivation for one skilled in the art to use the compositions in Hewitt et al. for the proposed treatment in the present invention. The invention described in Hewitt et al. requires a combined therapy approach in order to solve the problem outlined in that application or, minimally, CsA was meant to be included in the formulation. For instance, at column 3, lines 3-11, Hewitt et al., when observing the effects on skin allograft survival when animals were prevented from ingesting CsA, "concluded that most of the enhancement observed with local CsA treatment was due to the animals' ingestion of CsA from the treated area."

Thus, Hewitt et al. would be expected to teach that, at a bare minimum, a working formulation must include CsA to be effective for the identified conditions. Whatever additional beneficial effects observed by including immunosuppressants in the formulation of Hewitt's

invention, it must be presumed that Hewitt et al. intended the formulation to include CsA.

The Examiner cites column 9, lines 19-21, which states:

"Likewise, some conditions may require topical immunosuppressant application alone, without prior systemic CsA treatment."

Examiner has raised the quoted text above in an effort to argue that Hewitt et al. teaches that some conditions may require topical immunosuppression alone. Applicant respectfully asserts that this alone is not determinative of the intention of Hewitt et al. to consider immunosuppressant therapy alone in the application. There is no other mention, nor working examples, nor embodiments, depicting the reasoning asserted by Examiner. The entirety of Hewitt et al. is dedicated to the notion of pharmaceutical formulations, in specified amounts by weight, of CsA with other immunosuppressants and anti-inflammatory agents, which necessarily combine to engage in site-specific immunosuppression.

It would run counter to the reasoning outlined in Hewitt et al. to only treat with one immunosuppressant. For example, Figure 4 of the Hewitt application describes skin allograft experiments which utilize CsA for the treatment methodology. Hewitt et al. describes both the in vitro and in vivo experiments as demonstrating "that prior systemic cyclosporine treatment sensitizes both basal and activated immunocytes to become more responsive to

secondary exposure to immunosuppressants for increased efficacy at a local level." See column 11, lines 4-8.

Furthermore, Hewitt et al. describe data which show "that to inhibit an ongoing inflammatory immune response, a key factor is that cyclosporine must be delivered locally at high concentrations (>10,000 ng/gm or ml) during primary topical treatment." See column 11, lines 12-16. As a result, a necessary component to any of the formulations considered by Hewitt et al. must include CsA. Without CsA in the formulation, none of the benefits to treatment with Hewitt's composition could be achieved.

Examiner finds that because Lozada discusses use of azathioprine as a method of treatment, the present application is obvious over such use. However, Applicant respectfully submits that Lozada in fact teaches away from the present application. The purpose of Lozada was to assess the clinical significance of an alleged synergistic effect when using a corticosteroid (prednisone) in combination with an immunosuppressant (azathioprine). See Lozada, page 257. This paper was meant to provide an analysis based on a side-to-side comparison of the clinical benefits with the side effects from treating patients suffering from vesiculoerosive oral diseases with prednisone and azathioprine together. In fact, it was known at the time of Lozada that azathioprine is absorbed at the gastrointestinal level.

Moreover, toxicity had been observed which was caused by azathioprine, leading to bone marrow depression manifested as leucopenia and bleeding. Additionally, long

term use of azathioprine was believed to increase the risk of malignancy. Thus, in view of Lozada, one skilled in the art at the time would not have been expected to consider a treatment protocol involving on azathioprine. This was due to the inherent risks of treatment with immunosuppressants alone. Lozada does consider using prednisone + azathioprine, but this combination is not claimed in the present invention.

As with Hewitt et al., the Examiner considers Sharpe et al. rendering the present application obvious merely because the inventors considering using azathioprine as one of several immunosuppressants to be used in the treatment of a condition. However, as with Hewitt, Applicant respectfully submits that the invention described in Sharpe et al. refers to a combination therapy involving a corticosteroid and an immunosuppressant. Furthermore, Sharpe focuses the treatment regimen on disorders mediated by proteases which result in skin or mucosal lesions. This listed class of disorders is distinct from the graft versus host disease target of the present application.

There would be no motivation for one skilled in the art at the time to combine Hewitt, Lozada and Sharpe in order to arrive at the present invention. These references merely raise azathioprine as an immunosuppressant to be utilized in conjunction with a corticosteroid. There is no consideration given by any of the above references to use azathioprine alone. In fact, these references teach away from such use, as the toxic effects of azathioprine were well known at the time. This toxicity was considered by these references, which lead to the combination approach.

Under MPEP §2145, it is improper for the Examiner to use impermissible hindsight to "pick and choose" from various methods across several references in order to arrive at the claimed invention. This is especially apparent when Batt et al. is considered along with the above identified references. Batt et al. describes use of quinolines alone or in combination with immunosuppressive agents, one of those being azathioprine.

As discussed above, the mere fact that a reference mentions azathioprine for use in treatment of a particular disease is not determinative of obviousness. As Examiner is well aware, there must be a suggestion to combine references and in the absence of such suggestion, the obviousness rejection is considered improper.

None of the cited references mention treatment using azathioprine alone and, in fact, the references describe the necessity of a combined therapy of corticosteroid + immunosuppressant or, at the very least, treatment using the corticosteroid alone. Treatment using only the immunosuppressant was never considered in any of the cited references.

Therefore, Applicant respectfully requests Examiner withdraw the §103 rejection. There would be no motivation for one skilled in the art to combine the listed references, as these teach away from use of azathioprine alone for treatment of graft versus host, especially in the manner described in the present application.

Applicant respectfully requests withdrawal of the above identified rejections and allowance of the present application based on Applicant's arguments and amendments. If there are any questions or comments, Applicant's attorney may be reached at the telephone number state below.

Respectfully submitted,

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